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K.L. RINEHART et al.: "AMINOCYCLITOL ANTIBIOTICS, ACS Symposium Series 125, American Chemical Society, 1980, WASHINGTON D.C. (US), pages 1-11 "An introduction"

(73) Proprietor: **SANDOZ AG**
Lichtstrasse 35
CH-4002 Basel (CH)
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(73) Proprietor: **SANDOZ-PATENT-GMBH**
Humboldtstrasse 3
D-7850 Lörrach (DE)
(84) **DE**

(72) Inventor: **Loibner, Hans**
Heimgasse 23
A-1238 Vienna (AT)
Inventor: **Streicher, Wolfgang**
Gergheidengasse 6/4
A-1130 Vienna (AT)
Inventor: **Stütz, Peter**
Nästlbergergasse 15
A-1130 Vienna (AT)

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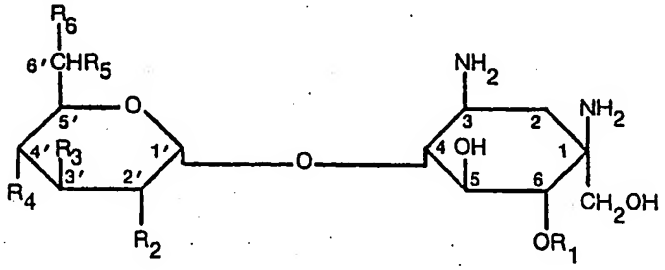
Description

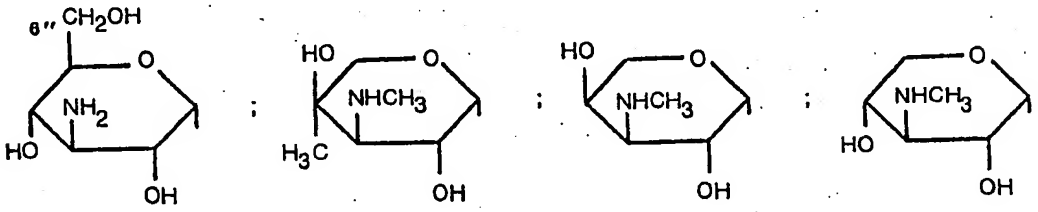
The present invention concerns aminoglycoside derivatives processes for their production, pharmaceutical compositions containing them and such derivatives for use as pharmaceuticals.

In particular the invention concerns compounds of formula I



I

wherein R_1 represents hydrogen or a group of formula

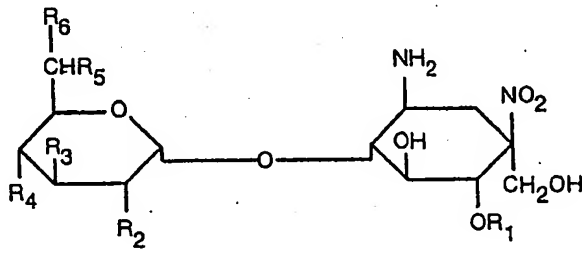


II IIa IIb IIc

R_2 represents hydroxy or amino,
R_3 represents hydrogen or hydroxy,
R_4 represents hydrogen or hydroxy,
R_5 represents amino, methylamino, dimethylamino or, when R_2 represents amino also hydroxy and
R_6 represents hydrogen or methyl in free base form or in the form of an acid addition salt.

According to the invention these compounds can be prepared

a) by reducing a compound of formula III



III

wherein R_1 to R_6 are as defined above, and amino groups, where present, may be protected, and if required deprotecting any protected amino groups still present in the compound thus obtained, or

b) to produce a compound wherein R_5 represents methylamino or dimethylamino, mono- or di-methylating a corresponding compound of formula I wherein R_5 represents amino or mono-methylating a corresponding compound wherein R_5 represents methylamino, whereby other amino groups, where present may be protected, and if required deprotecting any protected amino groups in the compound thus obtained; and recovering the compound of formula I thus obtained in free form or in the form of an acid addition salt as required.

Process a) can be carried out in a manner conventional for such reductions such as described in Houben-Weyl Bd. 4/lc, for example, using Raney-Nickel and hydrogen in an inert solvent such as an alcohol e.g. methanol. Raised pressure can be advantageous.

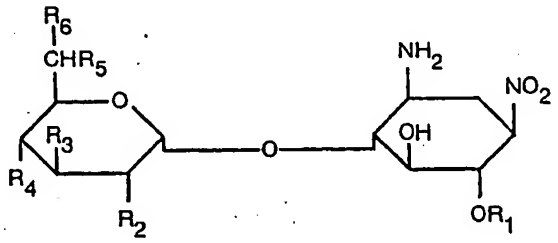
Process b) can be effected using conventional methylating agents. For example for introduction of a single methyl group in a compound containing a 6'-NH_2 group this is first reacted selectively with a carbonic acid derivative of formula X—$COOR_7$ wherein X represents a reactive group and R_7 represents alkyl or aralkyl to produce the corresponding $NHCOOR_7$ derivative which is then reduced in conventional manner, e.g. with a complex metal hydride e.g. $LiAlH_4$. Introduction of two methyl groups in compounds containing a 6'-NH_2 group can for example be carried out by protecting all amino groups except that at 6'-,

introducing methyl groups in conventional manner e.g. by reaction with formaldehyde in the presence of a reducing agent or of NaH_2PO_3 and then deprotecting the end product. Introduction of a further methyl group in a 6'-methylamino compound may be effected analogously in conventional manner.

Suitable protecting groups are for example benzyloxycarbonyl, tert.butoxycarbonyl or trichlorethoxycarbonyl. These groups can be introduced and removed in conventional manner such as for example analogously to the methods described hereinafter in the examples.

The compounds of the formula I may be converted in conventional manner into their acid addition salts and vice versa.

The starting materials of formula III can be prepared by reacting a compound of formula IV

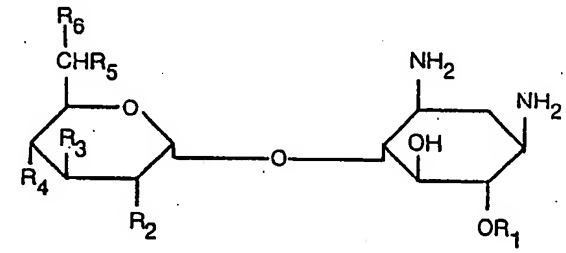


IV

wherein R_1 to R_6 are as defined above,
amino groups being optionally protected, with formaldehyde and if required deprotecting any protected amino groups in the compound thus obtained.

This reaction may be carried out in conventional manner in a solvent inert under the reaction conditions e.g. a lower alcohol such as methanol or a chlorinated hydrocarbon such as chloroform and in the presence of a base such as a tertiary amine e.g. triethylamine. Temperatures conveniently lie between room temperature and the boiling point of the reaction mixture. The compounds thus obtained can, of course, be further reacted directly e.g. in situ according to process a). Direct further reaction is preferred.

The compounds of formula IV can be obtained by oxidising a compound of formula V



V

wherein R_1 to R_6 are as defined above,
and all amino groups, with the exception of that in position 1, are protected. This oxidation can take place in conventional manner e.g. as described in J. Org. Chem. *44*/659 (1979) or with $KMnO_4$. Once again the resulting products may optionally be deprotected or, preferably, directly reacted further to compounds of formula III.

The compounds of the formula V are known, can be obtained as referred to in the literature (cf. Merck Index 4th Edition, pp. 565 and 692) or are available commercially. They can be employed in the form of mixtures such as those obtained when preparation is by fermentative methods (e.g. gentamicin C_2/C_{2a}—4/1 to 3/2). Reaction of these compounds will lead in turn to mixtures of compounds IV, III or I respectively. Such mixtures can be separated into their individual components at any stage of the preparative chain, but this is preferably carried out on deprotected end products of formula I. The methods employed in separation are conventional such as described in USP 3,984,395 or K. Byrne et. al. J. Chromatogr. *131*/191 (1977).

The compounds of formulae III and IV are new and the former also form part of the invention.

All intermediate and end products can be isolated and purified according to known methods.

The compounds of formula I possess chemotherapeutic, in particular antimicrobial activity as indicated in vitro in series dilution tests and in vivo in tests on mice using various bacterial strains such as e.g. Staph. aureus, Staph. epidermis, Haemophilis spp., Pseudomonas aeruginosa, E. coli, Proteus vulgaris, proteus mirabilis, Proteus morganii, Enterobacter cloacae, Klebsiella pneumonias and Serratia marcescens. This activity is observed in vitro at concentrations between ca. 0.05 to 50 µg/ml and in vivo at between ca. 0.4 and 100 mg/kg animal body weight. They are particularly effective in aminoglycoside resistant strains and have thus a broad spectrum of activity.

The compounds are thus indicated for use as anti-bacterially active antibiotics.

An indicated suitable daily dosage for use as anti-bacterially active antibiotic is from about 0.1 to 2 g. If desired this may be administered in divided doses 2 to 4 times a day in unit dosage form containing about 25 to 1500 mg of the compound or in sustained release form.

The compounds may be used in free base form or in the form of chemotherapeutically acceptable acid addition salts e.g. as the penta hydrochloride. Such salt forms exhibit the same order of activity as the free base forms.

The compounds may be admixed with conventional chemotherapeutically acceptable diluents and carriers, and, optionally, other excipients and administered in such forms as tablets, capsules or injectable preparations.

Such compositions also form part of the invention.

The invention therefore also concerns a method of combatting bacteria comprising administering to a subject in need of such treatment an effective amount of a compound of formula I or a chemotherapeutically acceptable acid addition salt thereof and such compounds for use as chemotherapeutic agents, in particular anti-bacterially active antibiotics.

Preferred meanings for the substituents are

R_1 = a) formula IIa
b) formula II

R_2 = a) hydroxy or amino
b) amino

R_3+R_4 = a) hydrogen
b) hydroxy

R_5 = a) amino, mthylamino, dimethylamino
b) amino or when R_2 represents amino also hydroxy

R_6 = a) hydrogen or amino
b) hydrogen; as well as combinations of these

A particular group of compounds according to the invention is that wherein

R_1 represents a group of formula IIa,
R_2 represents amino,
R_3 and R_4 represent hydrogen and
R_6 represent hydrogen or methyl and
R_5 represents amino, methylamino or dimethylamino.

Another interesting group covers those compounds wherein
R_1 represents a group of formula II,
R_2 represents hydroxy or amino,
R_3 and R_4 represent hydroxy,
R_5 represents amino or when R_2 represents amino also hydroxy and
R_6 represents hydrogen.

A particularly preferred single compound is 1-C-hydroxymethylgentamicin C_2 in free base form or acid addition salt form preferably pentahydrochloride or sulfate salt form.

The following examples illustrate the invention. All temperatures are in degrees centigrade.

Example 1

1-C-Hydroxymethylgentamicin C_2. Pentahydrochloride (compound no. 1 — process a)

0.64 g of 3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_2 are dissolved in 5 ml of methanol and after cooling to −7° reacted with 0.3 ml of triethylamine. After 5 mins the solution is poured into 10 ml of 37% formaldehyde solution and raised to room temperature. After dilution with water and acidification with 0.1 N HCl the solution is extracted with dichloromethane and the organic phase concentrated on a rotary evaporator. The substance having R_f = 0.56 (in dichloromethane/methanol = 10/1) is isolated by chromatography on silica gel with dichloromethane/methanol (100/2—4). The resulting compound is reduced with hydrogen at 4 atm. using a Raney-Nickel suspension in 20 ml of methanol. After filtration of the catalyst the solution is concentrated on a rotary evaporator and the residue taken up with ethyl acetate, washed with 2N ammonia solution and concentrated on a rotary evaporator. This residue is taken up in 5 ml of trifluoroacetic acid and mixed after 3 minutes with 100 ml of diethylether. The precipitate is filtered off and converted to the (penta)hydrochloride using Amberlite® IRA 401 S ion exchange resin, R_f = 0.53 (dichloromethane/methanol/25% ammonia = 2/2/1).

C—13 NMR: 102, 8; 96, 0; 85, 8; 78, 0; 73, 2; 70, 7; 69, 8; 68, 9; 67, 0; 64, 1; 60, 7; 59, 3; 50, 4; 49, 6; 48, 2; 35, 2; 29, 8; 23, 0; 21, 7; 21, 2; 13, 5.

Example 2

1-C-Hydroxymethylgentamicin C_{1a}.Pentahydrochloride (compound No. 2 — process a)

0.8 g of 3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_{1a} are dissolved in 20 ml of chloroform, reacted with 10 g of paraformaldehyde and 1 ml of triethylamine and refluxed for 30 minutes. The resulting mixture is filtered under suction and the mother liquor chromatographed over silica gel with ethylacetate/hexane (2/1). $R_f = 0.5$ (in dichloromethane/methanol = 9/1). The resulting product is reduced with hydrogen at 4 atm. using a Raney-Nickel suspension in 30 ml of methanol. Filtration of the catalyst yields an anorphous foam which is dissolved in 10 ml of trifluoroacetic acid and after 7 minutes added to 200 ml of diethylether. The precipitate is filtered under suction and chromatographed over silica gel with chloroform/methanol/30% ammonia (70/26/9). The product having $R_f = 0.13$ in the above eluant is collected and converted by acidification with methanolic hydrochloric acid and precipitation with diethylether into the (penta)hydrochloride.

H—NMR, characteristic signals: 1,37 s, 3H; 2, 72 dd, J_1=14, J_2=3, 5, 1H; 2, 96 s, 3H; 5, 15 d, J=3, 6, 1H; 5. 85 d. J=3. 6, 1H.

Analogously to the above Examples 1 and 2 or as otherwise herein described, the following compounds may be obtained from the appropriate starting materials:

1-C-Hydroxymethylgentamicin C_1.pentahydrochloride (compound no. 3).

C—13 NMR: 103, 1; 95, 5; 86, 1; 77, 6; 73, 7; 71, 1; 70, 3; 69, 1; 67, 5; 64, 7; 61, 1; 59, 8; 58, 7; 49, 9; 48, 6; 35, 6; 32, 3; 30, 2; 24, 4; 22, 1; 21, 8; 10, 5.

1-C-Hydroxymethylgentamicin C_{2a}.pentahydrochloride (compound no. 4).

H—NMR, characteristic signals: 1,34 d, J=7, 3H; 1, 37 s, 3H; 2, 72 dd, J_1=13, 5, J_2=3, 5, 1H; 2, 96 s, 3H; 5, 12 d, J=3, 6, 1H; 5, 91 d, J=3, 6, 1H.

1-C-Hydroxymethylgentamicin C.pentahydrochloride (compound no. 5).

1-C-Hydroxymethylgentamicin C_2/C_{2a}.pentahydrochloride (compound no. 6).

Compound no. 6 is obtained from starting materials themselves derived from fermatatively produced gentamicin C_2/C_{2a} (ca 4/1) and can be resolved as follows:

300 mg of 1-C-Hydroxymethylgentamicin C_2/C_{2a}.pentahydrochloride are dissolved in water and this solution introduced onto a middle pressure column (1.5 m × 1.6 cm) filled with CG 50 I ion exchange resin (NH_4^+-form). Elution with ca 1 litre of water follows (flow 20 ml/minute, pressure 4—5 bar). This is followed by gradient elution over 90 minutes from water to 0.4 N ammonia. The fractions containing the product are concentrated individually on a rotary evaporator. The first 5 fractions contain according to 250 MHz H—NMR the desired C_2 derivative in 95% purity.

Example 3

1-C-Hydroxymethyl-6'-N-methylgentamicin C_{1a}.pentahydrochloride (compound no. 7 — process b)

1.63 g of 1-C-Hydroxymethylgentamicin C_{1a} (free base) are dissolved in 30 ml of methanol and a solution of 1.06 g of N-benzyloxycarbonyloxy)-5-norbornene-2,3-dicarboxylic acid imide in 20 ml of methanol and 5 ml of dichloro-methane added at −20°. After 1 hour the mixture is concentrated on a rotary evaporator and the residue chromatographed on silica gel with chloroform/methanol/25% ammonia (15/4/1). The product with $R_f = 0.45$ (in chloroform/methanol/30% ammonia = 70/21/9) is collected. 250 mg of the 1-C-hydroxymethyl-6'-carbobenzoxygentamicin C_{1a} thus obtained are dissolved in 25 ml of abs. tetrahydrofuran and under an argon atmosphere lithium aluminium hydride added until gas evolution ceases. The mixture is then refluxed for 1 h. The excess reducing agent is destroyed with methanol and the reaction mixture acidified with acetic acid, the precipitate filtered off and the clear filtrate concentrated on a rotary evaporator. The residue is dissolved in 10 ml of water and then eluted over CG 50 I ion exchange resin (NH_4^+-form) initially with water and then gradually with water to 0.5 N ammonia.

The fractions containing the product are concentrated, the residue dissolved in methanolic hydrochloric acid and the title product precipitated with diethylether. $R_f = 0.2$ (in chloroform/methanol/30% ammonia = 70/26/9).

H—NMR, characteristic signals: 1, 35 s, 3H; 2, 70 dd, J_1=14, J_2=3, 5, 1H; 2, 78 s, 3H; 2, 95 s, 3H; 5, 12 d, J=3, 6, 1H; 5, 84 d, J=3, 6, 1H.

Example 4

1-C-Hydroxymethyl-6'-N-dimethylgentamicin C_{1a}.sulphate (compound 8 — process b)

400 mg 1-Hydroxymethyl-6'-carbobenzoxygentamicin C_{1a} are dissolved in 10 ml of methanol and 900 mg of di-tert.-butyldicarbonate and 0.2 ml of pyridine added. The mixture is stirred for 2 days at room temperature and then refluxed for 3 hrs. Concentration on a rotary evaporator is carried out followed by dissolution of the residue in diethylether and threefold trituration with 2 N ammonia. The organic phase is concentrated, dissolved in 10 ml of methanol, mixed with 500 mg of ammonium formate, 2 ml of water and 100 mg palladium 10% on charcoal and refluxed for 15 minutes. Extraction by shaking with water and ethylacetate follows and the resulting ethylacetate phase is dried and concentrated. The residue is dissolved in 10 ml dioxane, 10 ml of 1 N sodium dihydrogen phosphite solution and 3 ml of 33% formaldehyde solution added and the mixture warmed for 30 minutes at 65°. The pH is then adjusted to 11 with 1 N sodium hydroxide and extraction with chloroform is carried out three times.

The organic phase is dried and concentrated on a rotary evaporator and the residue dissolved in 5 ml of trifluoroacetic acid, mixed after 7 minutes with 100 ml of diethyl ether and the precipitate filtered off

under suction and washed with ether. The product is dissolved in 5 ml of water and converted to the sulphate in a column with Amberlite® IRA 401 S ion exchange resin (sulphate-form). $R_f = 0.30$ (in chloroform/methanol/30% ammonia = 70/26/9).

H—NMR, chararacteristic signals: 1, 38 s, 3H; 2, 7 dd, J_1=14, J_2=3, 5, 1H; 2, 97 s, 3H; 2, 99 s, 6H; 5, 18 d, J=3, 6, 1H; 5, 88 d, J=3, 6, 1H.

The required starting materials are prepared as follows:

A) *3,2',6',3''-Tetra-N-tert.butoxycarbonyl-1-desamino-1-nitrogentamicin C_2 (for example 1)*

To a solution of 17 g of 3,2',6',3''-tetra-N-tert.-butoxycarbonylgentamicin C_2 and 3.4 g 3-tert.-butyl-4-hydroxy-5-methylenephenylsulphide in 750 ml of 1,2-dichloroethane are added whilst boiling 34 g of 3-chloroperbenzoic acid in solid form. After 30 minutes the solution is concentrated on a rotary evaporator and the residue triturated with 20% $KHSO_3$, saturated $NaHCO_3$ and water and chromatographed over silica gel (ethylacetate/hexane = 3/2). The substance with R_f=0.17 (dichloromethane/methanol = 20/1) is isolated.

B) *3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_{1a} (for example 2)*

A mixture of 50 g potassium permanganate and 125 g potassium dihydrogenphosphate in 0.5 litre of water is brought to 75° and 25 g of 3,2',6',3''-tetra-N-tert.-butoxycarbonylgentamicin C_{1a} dissolved in 0.5 litre of acetone added in one gush. The mixture is refluxed for 3 minutes and poured into ice-water containing 150 g of sodium hydrogensulphite. The manganese dioxide is filtered off and the solution extracted with chloroform. After drying, the organic phase is concentrated on a rotary evaporator and the residue chromatographed over silica gel with ethylacetate/hexane = 3/2. A colourless foam is obtained. R_f = 0.16 (dichloromethane/methanol = 20/1).

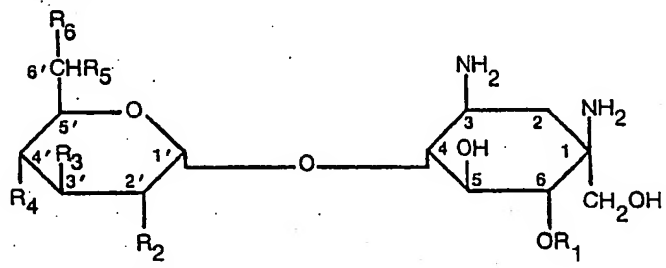
The following compounds may be obtained analogously:

3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_1. R_f = 0.74 (dichloromethane/methanol = 9/1.

3,2',6',3''-Tetra-N-tert.-butoxycarbonyl-1-desamino-1-nitrogentamicin C_{2a}. R_f = 0.17 (dichloromethane/methanol = 20/1)

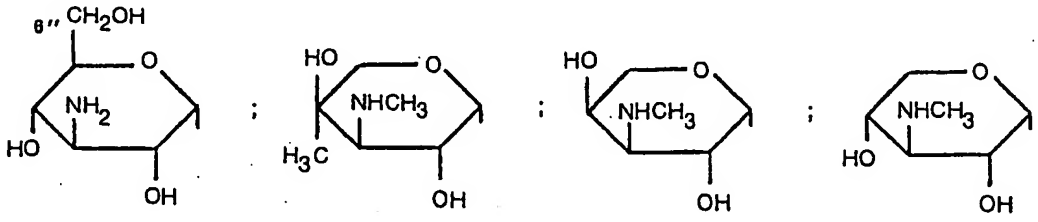
Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. Compounds of formula I



I

wherein R_1 represents hydrogen or a group of formula



II IIa IIb IIc

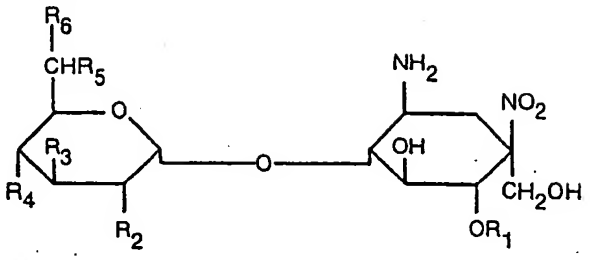
R_2 represents hydroxy or amino,
R_3 represents hydrogen or hydroxy,
R_4 represents hydrogen or hydroxy,
R_5 represents amino, methylamino, dimethylamino or, when R_2 represents amino also hydroxy and
R_6 represents hydrogen or methyl in free base form or in the form of an acid addition salt.

2. 1-C-Hydroxymethylgentamicin C_2 in free base form or in the form of an acid addition salt.

3. A compound according to Claim 2 in the form of its pentahydrochloride or sulphate.

4. A process for preparing a compound as claimed in any one of Claims 1 to 3 which comprises:

a) reducing a compound of formula III



III

wherein R_1 to R_6 are as defined above, and amino groups, where present, may be protected, and if required deprotecting any protected amino groups still present in the compound thus obtained, or

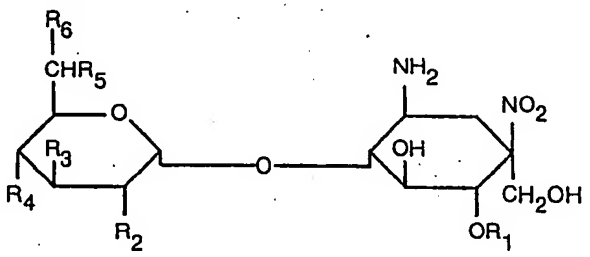
b) to produce a compound wherein R_5 represents methylamino or dimethylamino, mono- or di-methylating a corresponding compound of formula I wherein R_5 represents amino or mono-methylating a corresponding compound wherein R_5 represents methylamino, whereby other amino groups, where present may be protected, and if required deprotecting any protected amino groups in the compound thus obtained; and recovering the compound of formula I thus obtained in free form or in the form of an acid addition salt as required.

5. A pharmaceutical composition comprising a compound of formula I as claimed in Claim 1 or a chemotherapeutically acceptable salt thereof together with a chemotherapeutically acceptable diluent or carrier.

6. A compound of formula I as claimed in Claim 1 or a chemotherapeutically acceptable salt thereof for use as a pharmaceutical.

7. A compound of formula I as claimed in Claim 1 or a chemotherapeutically acceptable salt thereof for use as an anti-bacterially active antibiotic.

8. Compounds of formula III

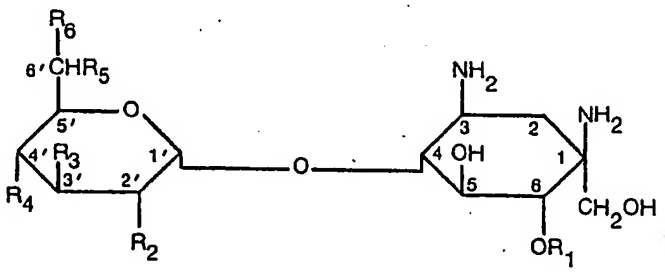


III

wherein R_1 to R_6 are as defined in claim 1.

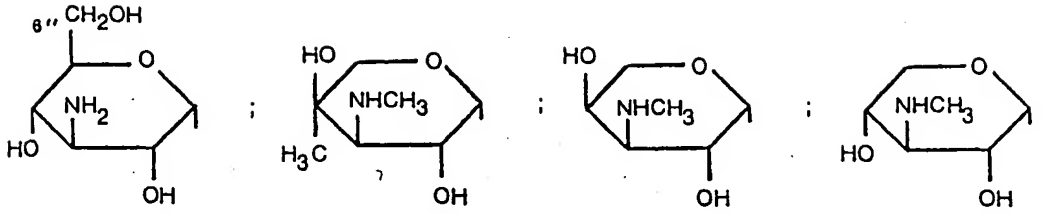
Claims for the Contracting State: AT

1. A process for preparing a compound of formula I



I

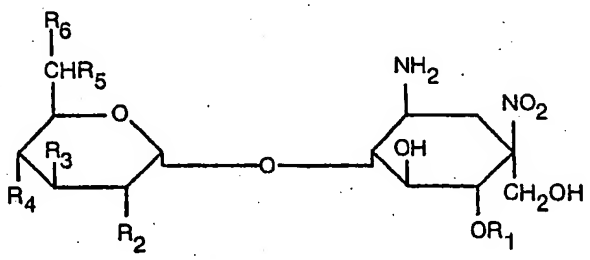
wherein R_1 represents hydrogen or a group of formula



II IIa IIb IIc

R_2 represents hydroxy or amino,
R_3 represents hydrogen or hydroxy,
R_4 represents hydrogen or hydroxy,
R_5 represents amino, methylamino, dimethylamino or, when R_2 represents amino also hydroxy and
R_6 represents hydrogen or methyl in free base form or in the form of an acid addition salt, which comprises:

a) reducing a compound of formula III



III

wherein R_1 to R_6 are as defined above, and amino groups, where present, may be protected, and if required deprotecting any protected amino groups still present in the compound thus obtained, or

b) to produce a compound wherein R_5 represents methylamino or dimethylamino, mono- or di-methylating a corresponding compound of formula I wherein R_5 represents amino or mono-methylating a corresponding compound wherein R_5 represents methylamino, whereby other amino groups, where present may be protected, and if required deprotecting any protected amino groups in the compound thus obtained; and recovering the compound of formula I thus obtained in free form or in the form of an acid addition salt as required.

2. A process as claimed in Claim 1 wherein the compound prepared is 1-C-hydroxymethylgentamicin C2 in free base form or in the form of an acid addition salt.

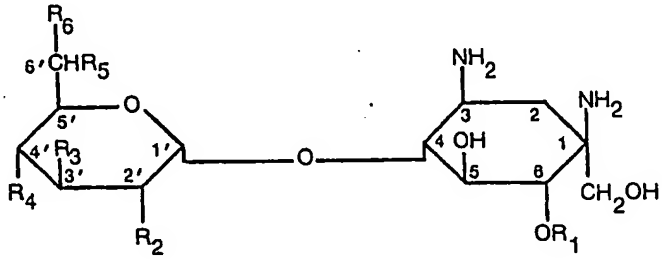
3. A process as claimed in Claim 2 wherein the acid addition salt form is the pentahydrochloride or sulphate.

4. A pharmaceutical composition comprising a compound prepared according to any one of Claims 1 to 3 in free base form or in the form of a chemotherapeutically acceptable acid addition salt thereof together with a chemotherapeutically acceptable diluent or carrier.

5. A compound as prepared according to any one of Claims 1 to 3 in free base form or in the form of a chemotherapeutically acceptable acid addition salt for use as a pharmaceutical.

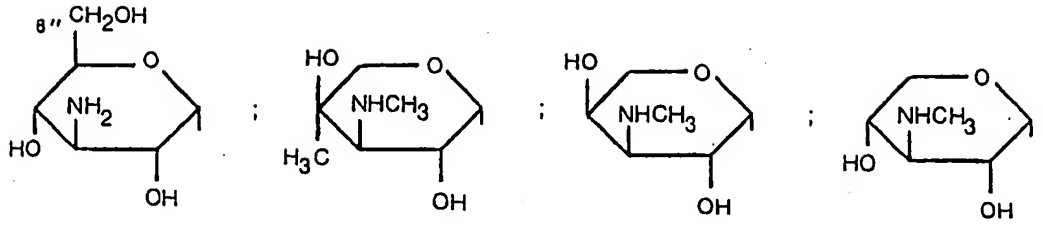
6. A compound as prepared according to any one of Claims 1 to 3 in free base form or in the form of a chemotherapeutically acceptable acid addition salt for use as an anti-bacterially active antibiotic.

7. A process for the preparation of a pharmaceutical composition comprising admixing a compound of formula I



I

wherein R_1 represents hydrogen or a group of formula

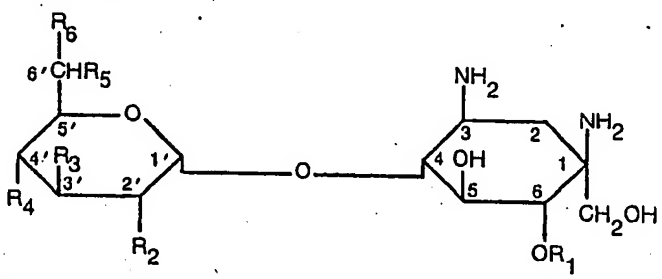


II ; IIa ; IIb ; IIc

R_2 represents hydroxy or amino,
R_3 represents hydrogen or hydroxy,
R_4 represents hydrogen or hydroxy,
R_5 represents amino, methylamino, dimethylamino or, when R_2 represents amino also hydroxy and
R_6 represents hydrogen or methyl in free base form or in the form of a chemotherapeutically acceptable addition salt thereof with a chemotherapeutically acceptable diluent or carrier.

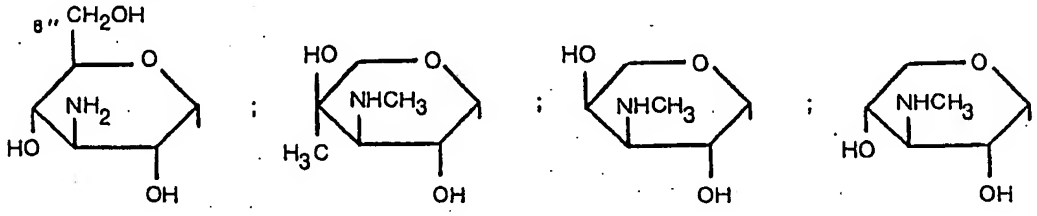
Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL SE

1. Verbindungen der Formel I



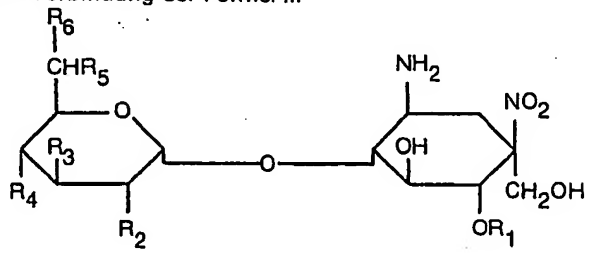
I

worin R_1 wasserstoff oder eine Gruppe der Formel



II ; IIa ; IIb ; IIc

darstellt,
R_2 Hydroxy oder Amino darstellt,
R_3 Wasserstoff oder Hydroxy darstellt,
R_4 Wasserstoff oder Hydroxy darstellt,
R_5 Amino, Methylamino, Dimethylamino oder, wenn R_2 Amino darstellt auch Hydroxy darstellt, und
R_6 Wasserstoff oder Methyl darstellt in Form der freien Base oder in Form eines Säureadditionssalzes.
2. 1-C-Hydroxymethylgentamicin C_2 in Form der freien Base oder in Form eines Säureadditionssalzes.
3. Eine Verbindung gemäss Anspruch 2 in Form von deren Pentahydrochlorid oder Sulfat.
4. Ein Verfahren zur Herstellung einer Verbindung wie in einem der Ansprüche 1 bis 3 beansprucht, bestehend aus
a) Reduktion einer Verbindung der Formel III



III

worin R_1 bis R_6 wie oben definiert sind und Amino-Gruppen, wo vorhanden, geschützt sein können, und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen, die in der so erhaltenen Verbindung noch vorhanden sind, oder

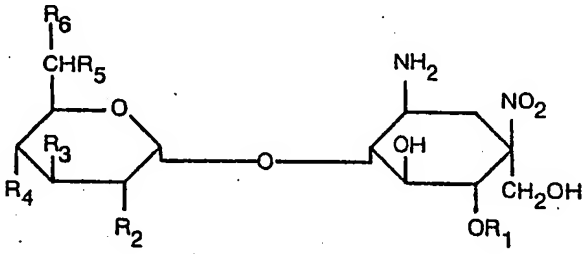
b) um eine Verbindung, worin R_5 Methylamino oder Dimethylamino darstellt, herzustellen, Mono- oder Dimethylierung einer entsprechenden Verbindung der Formel I worin R_5 Amino darstellt oder Monomethylierung einer entsprechenden Verbindung worin R_5 Methylamino darstellt, wobei andere Aminogruppen, wo vorhanden, geschütz sein können und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen in den so erhalten Verbindungen, und Gewinnung der so erhaltene Verbindung der Formel I in freier Form oder in Form eines Säureadditionssalzes.

5. Eine pharmazeutisch Zusammensetzung bestehend aus einer Verbindung wie im Anspruch 1 beansprucht oder einem chemotherapeutisch annehmbaren Salz davon zusammen mit einem chemotherapeutisch annehmbaren Verdünner oder Träger

6. Eine Verbindung der Formel wie im Anspruch 1 beansprucht oder ein chemotherapeutisch annehmbares Salz davon zur Verwendung als Pharmazeutikum.

7. Eine Verbindung der Formel I wie im Anspruch 1 beansprucht oder ein chemotherapeutisch annehmbares Salz davon zur Verwendung als antibakteriell wirksames Antibiotikum.

8. Verbindungen der Formel III

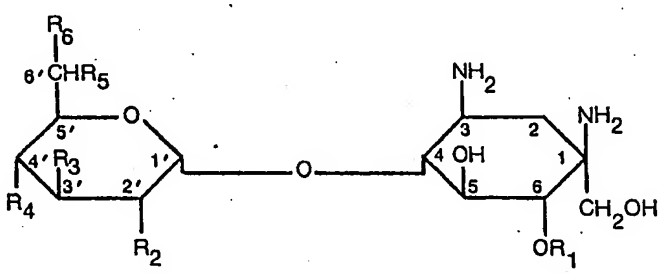


III

worin R_1 bis R_6 wie im Anspruch 1 definiert sind.

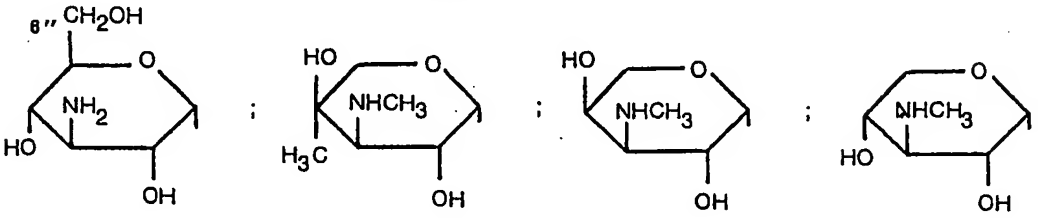
Patentansprüche für den Vertragsstaat: AT

1. Ein Verfahren zur Herstellung einer Verbindung der Formel I



I

worin R_1 wasserstoff oder eine Gruppe der Formel



II IIa IIb IIc

darstellt,

R_2 Hydroxy oder Amino darstellt,

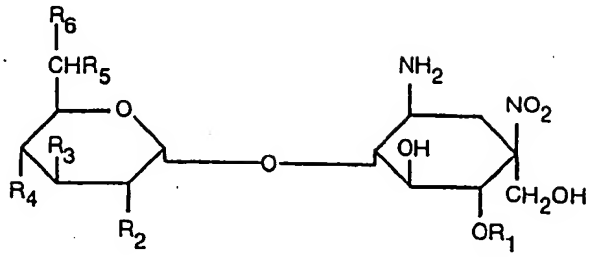
R_3 Wasserstoff oder Hydroxy darstellt,

R_4 Wasserstoff oder Hydroxy darstellt,

R_5 Amino, Methylamino, Dimethylamino oder, wenn R_2 Amino darstellt auch Hydroxy darstellt, und

R_6 Wasserstoff oder Methyl darstellt in Form der freien Base oder in Form eines Säureadditionssalzes bestehend aus

a) Reduktion einer Verbindung der Formel III



III

worin R_1 bis R_6 wie oben definiert sind und Amino-Gruppen, wo vorhanden, geschützt sein können, und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen, die in der so erhaltenen Verbindung noch vorhanden sind, oder

b) um eine Verbindung, worin R_5 Methylamino oder Dimethylamino darstellt, herzustellen, Mono- oder Dimethylierung einer entsprechenden Verbindung der Formel I worin R_5 Amino darstellt oder Monomethylierung einer entsprechenden Verbindung worin R_5 Methylamino darstellt, wobei andere Aminogruppen, wo vorhanden, geschütz sein können und wenn notwendig Entschützung etwaiger geschützter Amino-Gruppen in den so erhalten Verbindungen, und Gewinnung der so erhaltene Verbindung der Formel I in freier Form oder in Form eines Säureadditionssalzes.

2. Ein Verfahren wie im Anspruch 1 beansprucht, worin die hergestellte Verbindung 1-C-Hydroxymethylgentamicin C2 in Form der freien Base oder in Form eines Saureadditionssalzes ist.

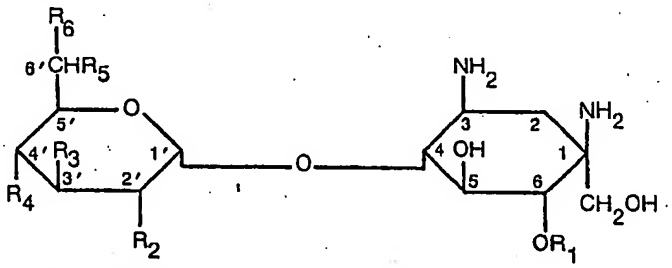
3. Ein Verfahren wie im Anspruch 1 beansprucht, worin die Säureadditionssalzform das Pentahydrochlorid oder Sulfat ist.

4. Ein pharmazeutische Zusammensetzung bestehend aus einer nach einem der Ansprüche 1 bis 3 hergestellten Verbindung in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Salzes davon zusammen mit einem chemotherapeutisch annehmbaren Verdünner oder Träger.

5. Eine nach einem der Ansprüche 1 bis 3 hergestellte Verbindung in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditionssalzes zur Verwendung als Pharmazeutikum.

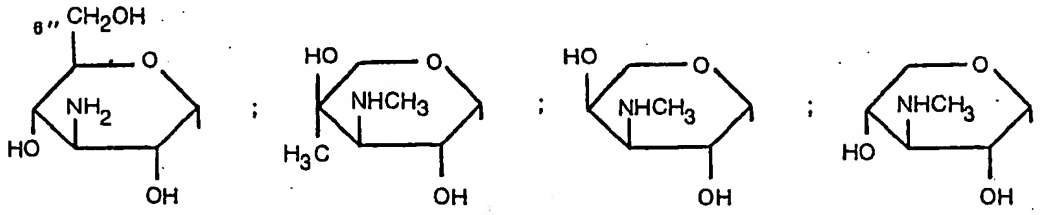
6. Eine nach einem der Ansprüche 1 bis 3 hergestellte Verbindung in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Saüreadditionssalzes zur Verwendung als antibakteriell wirksames Antibiotikum.

7. Ein Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung bestehend aus Beimischung einer Verbindung der Formel I



I

worin R_1 wasserstoff oder eine Gruppe der Formel



II' IIa IIb IIc

darstellt,

R_2 Hydroxy oder Amino darstellt,

R_3 Wasserstoff oder Hydroxy darstellt,

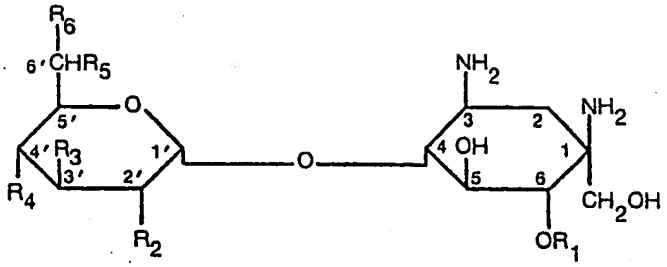
R_4 Wasserstoff oder Hydroxy darstellt,

R_5 Amino, Methylamino, Dimethylamino oder, wenn R_2 Amino darstellt auch Hydroxy darstellt, und

R_6 Wasserstoff oder Methyl darstellt in Form der freien Base oder in Form eines chemotherapeutisch annehmbaren Säureadditionssalzes mit einem chemotherapeutisch annehmbaren Verdünner oder Träger.

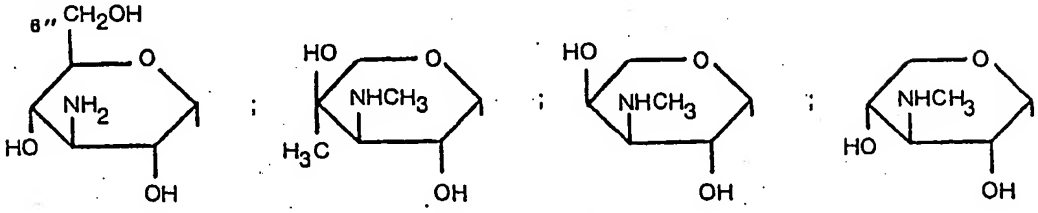
Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

1. Les composés de formule I



I

dans laquelle R_1 représente l'hydrogène ou un groupe de formule



II ; IIa ; IIb ; IIc

R_2 représente un groupe hydroxy ou amino,

R_3 représente l'hydrogène ou un groupe hydroxy,

R_4 représente l'hydrogène ou un groupe hydroxy,

R_5 représente un groupe amino, méthylamino, diméthylamino ou, lorsque R_2 représente un groupe amino, également un groupe hydroxy et

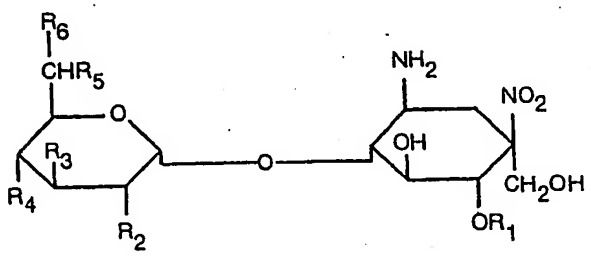
R_6 représente l'hydrogène ou un groupe méthyle, sous forme de base libre ou sous forme d'un sel d'addition d'acide.

2. La 1-C-hydroxyméthylgentamicine C_2 sous forme de base libre ou sous forme d'un sel d'addition d'acide.

3. Un composé selon la revendication 2 sous forme de son pentachlorhydrate ou sulfate.

4. Un procédé de préparation d'un composé tel que revendiqué à l'une quelconque des revendications 1 à 3, qui comprend:

a) la réduction d'un composé de formule III



III

dans laquelle R_1 à R_6 sont tels que définis ci-dessus, et des groupes amino, lorsqu'ils sont présents, peuvent être protégés, et si nécessaire la déprotection de tout groupe amino protégé encore présent dans le composé ainsi obtenu, ou

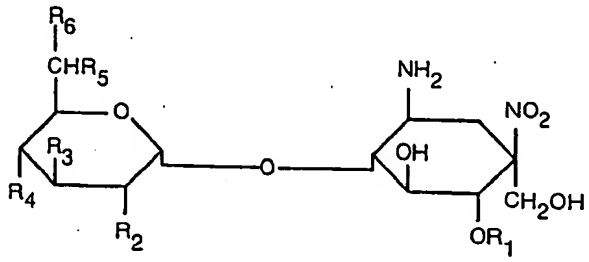
b) pour préparer un composé dans lequel R_5 représente un groupe méthylamino ou diméthylamino, la mono- ou la di-méthylation d'un composé de formule I correspondant dans lequel R_5 représente un groupe amino ou la mono-méthylation d'un composé correspondant dans lequel R_5 représente un groupe méthylamino, d'autres groupes amino, lorsqu'ils sont présents, pouvant être protégés, et si nécessaire la déprotection de tout groupe amino protégé dans le composé ainsi obtenu, et la récupération du composé de formule I ainsi obtenu, selon les besoins sous forme libre ou sous forme d'un sel d'addition d'acide.

5. Une composition pharmaceutique comprenant un composé de formule I tel que revendiqué à la revendication 1 ou un sel acceptable du point de vue chimiothérapeutique de ce composé, ensemble avec un diluant ou véhicule acceptables du point de vue chimiothérapeutique.

6. Un composé de formule I tel que revendiqué à la revendication 1 ou un sel acceptable du point de vue chimiothérapeutique de ce composé, pour l'utilisation comme médicament.

7. Un composé de formule I tel que revendiqué à la revendication 1 ou un sel acceptable du point de vue chimiothérapeutique de ce composé, pour l'utilisation comme antibiotique à activité anti-bactérienne.

8. Les composés de formule III

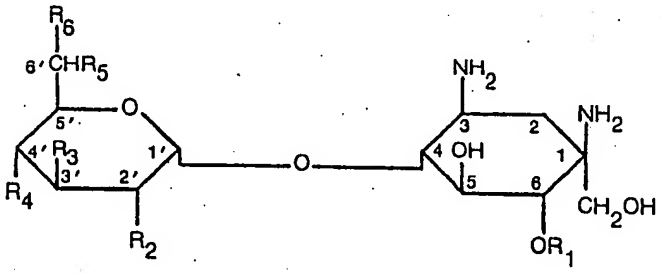


III

dans laquelle R_1 à R_6 sont tels que définis à la revendication 1.

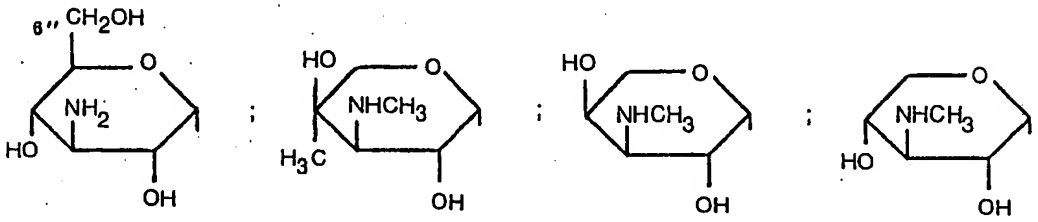
Revendications pour l'Etat contractant: AT

1. Un procédé de préparation d'un composé de formule I



I

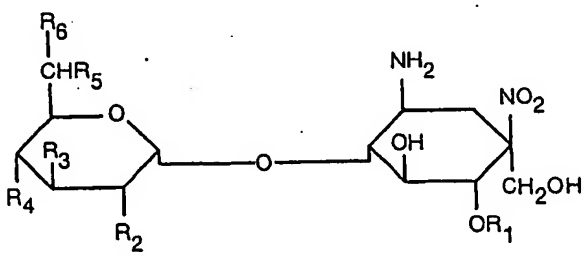
dans laquelle R_1 représente l'hydrogène ou un groupe de formule



II ; IIa ; IIb ; IIc

R_2 représente un groupe hydroxy ou amino,
R_3 représente l'hydrogène ou un groupe hydroxy,
R_4 représente l'hydrogène ou un groupe hydroxy,
R_5 représente un groupe amino, méthylamino, diméthylamino ou, lorsque R_2 représente un groupe amino, également un groupe hydroxy et
R_6 représente l'hydrogène ou un groupe méthyle, sous forme de base libre ou sous forme d'un sel d'addition d'acide, qui comprend:

a) la réduction d'un composé de formule III



III

dans laquelle R_1 à R_6 sont tels que définis ci-dessus, et des groupes amino, lorsqu'ils sont présents, peuvent être protégés, et si nécessaire la déprotection de tout groupe amino protégé encore présent dans le composé ainsi obtenu, ou

b) pour préparer un composé dans lequel R_5 représente un groupe méthylamino ou diméthylamino, la mono- ou la di-méthylation d'un composé de formule I correspondant dans lequel R_5 représente un groupe amino ou la mono-méthylation d'un composé correspondant dans lequel R_5 représente un groupe méthylamino, d'autres groupes amino, lorsqu'ils sont présents, pouvant être protégés, et si nécessaire la déprotection de tout groupe amino protégé dans le composé ainsi obtenu, et la récupération du composé de formule I ainsi obtenu, selon les besoins sous forme libre ou sous forme d'un sel d'addition d'acide.

2. Un procédé tel que revendiqué à la revendication 1, dans lequel le composé préparé est la 1-C-hydroxyméthylgentamicine C_2 sous forme de base libre ou sous forme d'un sel d'addition d'acide.

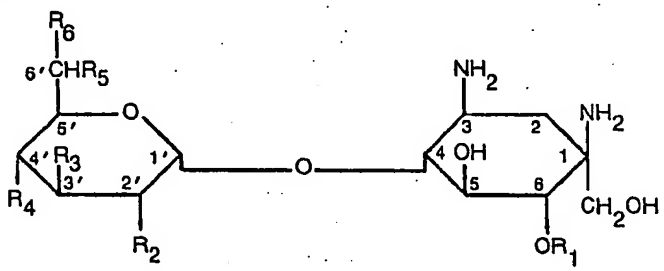
3. Un procédé tel que revendiqué à la revendication 2, dans lequel le sel d'addition d'acide est le pentachlorohydrate ou le sulfate.

4. Une composition pharmaceutique comprenant un composé préparé selon l'une quelconque des revendications 1 à 3 sous forme de base libre ou sous forme d'un sel d'addition d'acide de ce composé acceptable du point de vue chimiothérapeutique, ensemble avec un diluant ou véhicule acceptables du point de vue chimiothérapeutique.

5. Un composé préparé selon l'une quelconque des revendications 1 à 3 sous forme de base libre ou sous forme d'un sel d'addition d'acide acceptable du point de vue chimiothérapeutique, pour l'utilisation comme médicament.

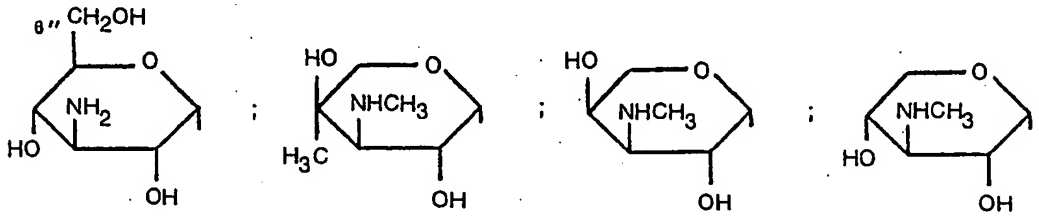
6. Un composé tel que préparé selon l'une quelconque des revendications 1 à 3, sous forme de base libre ou sous forme d'un sel d'addition d'acide acceptable du point de vue chimiothérapeutique, pour l'utilisation comme antibiotique à activité anti-bactérienne.

7. Un procédé de préparation d'une composition pharmaceutique comprenant l'admixtion d'un composé de formule



I

dans laquelle R_1 représente l'hydrogène ou un groupe de formule



II IIa IIb IIc

R_2 représente un groupe hydroxy ou amino,

R_3 représente l'hydrogène ou un groupe hydroxy,

R_4 représente l'hydrogène ou un groupe hydroxy,

R_5 représente un groupe amino, méthylamino, diméthylamino ou, lorsque R_2 représente un groupe amino, également un groupe hydroxy et

R_6 représente l'hydrogène ou un groupe méthyle, sous forme de base libre ou sous forme d'un sel d'additions d'acide de ce composé acceptable du point de vue chimiothérapeutique, avec un diluant ou véhicule acceptable du point de vue chimiothérapeutique.